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(54) Physiologically active polypeptide containing pharmaceutical composition

Ein physiologisch wirksames Polypeptid enthaltende pharmazeutische Zusammensetzung

Composition pharmaceutique contenant un polypeptide actif physiologiquement

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- **CHEMICAL ABSTRACTS, vol. 109, no. 4, 25 July 1988, Columbus, Ohio, US; abstract no. 27629T, HASUMI T. ET AL: 'Intranasal pharmaceutical compositions containing calcitonin and sucrose fatty acid esters' page 304 ;column 1 ; & JP-A-63 039 822 (YAMANOUCHI PHARMA CO LTD) 20 February 1988**
- **WORLD PATENTS INDEX LATEST Section Ch, Week 8708, Derwent Publications Ltd., London, GB; Class B, AN 87-053768 & JP-A-62 010 020 (KANEBO KK) 19 January 1987**
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Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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Description

Technical Field of the Invention

[0001] This invention relates to the use of a combination of an organic acid and a fatty acid sucrose ester as an absorption promoting agent in a physiologically active polypeptide-containing pharmaceutical composition in admixture with a conventional pharmaceutically acceptable carrier or diluent, which composition is suitable for oral administration or administration to the oral cavity.

Prior Art

[0002] Polypeptides such as insulin and calcitonin are water soluble high molecular weight compounds which are easily decomposed with stomach juice or intestine proteases (e.g. pepsin, trypsin), and hence, when these polypeptides are orally administered, they can not exhibit their physiological activities without being absorbed.

[0003] Accordingly, in order to exhibit the physiological activities, these polypetides are usually used in the form suitable for injection. However, such an administration form is not convenient and gives sometimes pain to the patients particularly when they must be administered at certain intervals or frequently.

[0004] - From the above viewpoint, it has been investigated to use the polypeptides in other administration forms than injection, and the present inventors have proposed a pharmaceutical composition suitable for administration by a vaginal route (Japanese Patent First Publication (Kokai) No. 294632/1989). Pharmaceutical composition for oral administration has also been proposed, for example, compositions incorporated with fatty acid sucrose esters (cf. Japanese Patent First Publication (Kokai) Nos. 10020/1987 and 33128/1987), but these compositions are still not sufficient in absorbability of the active ingredient.

[0005] Chemical Abstracts, vol. 109, no. 4, 25 July 1988, Columbus, Ohio, US; abstract no. 27629T, Hasumi, T. et al.: "Intranasal pharmaceutical compositions containing calcitonin and sucrose fatty acid esters" & JP-A-63039822 relates to a pharmaceutical composition for nasal administration which comprises calcitonin and a fatty acid sucrose ester contained in a liquid diluent or a carrier suitable for nasal administration, and is characterized by the use of the fatty acid sucrose ester as an absorption promoting agent. The fatty acid sucrose ester used therein includes an ester of a sucrose with a fatty acid having 6 to 18 carbon atoms such as caprylic acid, capric acid, myristic acid, palmitic acid, or stearic acid. The ester is contained in the composition in an amount of 0.1 to 30% by weight when the composition is liquid or semi-solid, or 0.1 to 90% by weight when the composition is solid.

[0006] The composition is characterized by the use of the fatty acid sucrose ester as an absorption promoting agent in a composition for nasal administration containing calcitonin, said ester being an alternative for a conventional surfactant, especially an ether type surfactant which has been shown to exert an excellent absorption promoting effect by destroying the nasal mucosa to accelerate a nasal drug permeation but not to be practical due to potent cytotoxicity as a sequence of tissue damage.

[0007] The pharmaceutical composition for nasal administration may be in the form of an aqueous solution, a hydrogel or a solid powder. The aqueous solution should preferably be at pH 3 to 5 in viewpoint of safety. A buffer used in the solution includes, for example, citric acid, tartaric acid, malic acid, and the like.

[0008] EP-A-0 302 772 discloses a nasal administration powder composition containing physiologically active peptide as an active ingredient and a water-soluble organic acid as an absorption promotor, and optionally a diluent. The water-soluble organic acid includes succinic acid, tartaric acid, citric acid, fumaric acid, etc. and is present in an amount of 0.05 to 99.995% by weight. The diluent used in EP-A-0 302 772 includes saccharoses, polysaccharides, dextrins, celluloses, etc.

[0009] World Patent Index Latest Section Ch, Week 8708, Derwent Publications Ltd., London GB; Class B, AN 87-053768 & JP-A-62010020 discloses a composition comprising calcitonin and a fatty acid sucrose ester having HLB value in a range of 11 to 16. By the use of such a fatty acid sucrose ester having a specific HLB value, calcitonin can efficiently be absorbed through the mucosa of the oral cavity. The fatty acid sucrose ester used in the composition includes an ester of sucrose with a fatty acid such as stearic acid, palmitic acid, oleic acid, or lauric acid.

[0010] Patent Abstracts of Japan, vol. 14, no. 126, 9 March 1990 & JP-A-2003609 discloses a sustained release preparation comprising nicardipin hydrochloride as an active ingredient, a fatty acid sucrose ester and an organic acid. Since nicardipin hydrochloride shows a short period of time for effective blood level and dissolves in a gastric juice but not in an intestinal juice, it is necessary to make nicardipin hydrochloride being soluble in an intestinal juice for preparing a sustained release preparation of this drug. In order to solve this problem, a mono-ester type fatty acid sucrose ester and an organic acid are used to dissolve nicardipin hydrochloride in an intestinal juice. Accordingly, a combination of the fatty acid sucrose ester and the organic acid is used for attaining solubility of nicardipin hydrochloride in an intestinal juice but not for promoting an absorption in an intestinal tract.

Brief Description of the Invention

[0011] According to the intensive studies by the present inventors, it has been found that by incorporating a combination of an organic acid and a fatty acid sucrose ester as an absorption promoting agent into the composition, the physiologically active polypeptide can effectively be absorbed via intestinal tract or mucous membrane in the oral cavity, and hence, the composition is useful for oral administration or for administration to the oral cavity.

[0012] An object of the invention is to provide a physiologically active polypeptide-containing pharmaceutical composition which is suitable for oral administration or for admostration to the oral cavity. Another object of the invention is to promote the absorption of the physiologically active polypeptide through the intestinal tract or mucous membrane in the oral cavity by using a combination of an organic acid and a fatty acid sucrose ester as an absorption promoting agent. A further object of the invention is to provide a rapidly soluble composition suitable for application to the oral cavity. These and other objects and advantages of the invention will be apparent to those skilled in the art from the following description.

Brief Description of Drawing

[0013]

Fig. 1 is a graph showing the effects for promoting absorption of human calcitonin (h-CT) by a combination of various fatty acid sucrose esters and tartaric acid.

Fig. 2 is a graph showing the effects for lowering calcium in serum accompanied to the h-CT absorption promoting effects by a combination of various fatty acid sucrose esters and tartaric acid.

Fig. 3 is a graph showing comparison in the serum calcium lowering effects between the use of a combination of sucrose laurate and tartaric acid, and the use thereof alone.

Fig. 4 is a graph showing comparison in the effects for promoting absorption of h-CT between the use of a combination of sucrose laurate and tartaric acid, and the use thereof alone.

Fig. 5 is a graph showing the effects for promoting absorption of a thyroid-stimulating hormone by a combination of sucrose stearate and tartaric acid.

Fig. 6 is a graph showing the effects for promoting absorption of an adrenocorticotrophic hormone by a combination of sucrose palmitate and tartaric acid.

Fig. 7 is a graph showing the effects for promoting absorption of calcitonin in a sublingual tablet.

Fig. 8 is a graph showing the effects for promoting absorption of calcitonin by a combination of various fatty acid sucrose esters and tartaric acid in a rapidly soluble composition.

Detailed Description of the Invention

[0014] The physiologically active polypeptide-containing pharmaceutical composition comprises as an active ingredient an effective amount of a physiologically active polypeptide, an absorption promoting agent consisting of a combination of an organic acid and a fatty acid sucrose ester in admixture with the conventional pharmaceutically acceptable carrier or diluent, which is suitable for oral administration or for administration to the oral cavity.

[0015] The organic acid used as one of the absorption promoting agent includes acetic acid, butyric acid, fumaric acid, malonic acid, phthalic acid, propionic acid, glutaric acid, adipic acid, valeric acid, caproic acid, maleic acid, ascorbic acid, isoascorbic acid, malic acid, succinic acid, lactic acid, tartaric acid, citric acid, and benzoic acid, among which the preferred ones are tartaric acid, citric acid, malic acid, lactic acid, benzoic acid and succinic acid. These organic acids may be used alone or in combination of two or more thereof. The amount of the organic acids may vary depending on the kinds of the preparation, but in case of a composition for oral administration, it is used in an amount of 0.1 to 70 % by weight, preferably 1 to 50 % by weight, based on the whole weight of the composition. In case of a composition suitable for administration to the oral cavity (sublingual tablet), it is used in an amount of 0.1 to 30 % by weight, preferably 2 to 20 % by weight, based on the whole weight of the composition. Besides, in case of a rapidly soluble preparation for application to the oral cavity, it is used in an amount of 30 to 90 % by weight, preferably 50 to 80 % by weight, based on the whole weight of the preparation (in the lyophilized form).

[0016] The fatty acid sucrose ester includes sucrose stearate, sucrose palmitate, sucrose oleate, sucrose laurate, sucrose behenate, and sucrose erucate, among which the preferred ones are sucrose stearate, sucrose palmitate, sucrose oleate, and sucrose laurate. These fatty acid sucrose esters may be used alone or in combination of two or more thereof. The amount of the fatty acid sucrose esters may vary depending on the kinds of the preparation, but in case of a composition for oral administration, it is used in an amount of 0.1 to 50 % by weight, preferably 0.5 to 30 % by weight, based on the whole weight of the composition. In case of a composition suitable for administration to the oral cavity (sublingual tablet), it is used in an amount of 0.1 to 20 % by weight, preferably 1 to 10 % by weight, based

on the whole weight of the composition. Besides, in case of a rapidly soluble preparation for administration to the oral cavity, it is used in an amount of 5 to 50 % by weight, preferably 15 to 35 % by weight, based on the whole weight of the preparation (in the lyophilized form).

[0017] The physiologically active polypeptides used in the invention are polypeptides having a comparatively low molecular weight. Suitable examples of the physiologically active polypeptides are, insulin, angiotensin, vasopressin, desmopressin, LH-RH (luteinizing hormone-releasing hormone), somatostatin, calcitonin, glucagon, oxytocin, gastrins, somatomedins, secretin, h-ANP (human atrial natriuretic peptide or factor), ACTH (adrenocorticotropic hormone), MSH (melanocyte-stimulating hormone), β-endorphin, muramyl dipeptide, enkephalins, neurotensin, bombesin, VIP (vasoactive intestinal polypeptide), CCK-8 (cholecystokin-8), PTH (parathyroid hormone), CGRP (calcitonin gene related peptide), TRH (thyrotropin releasing hormone), endothelin, TSH (thyroid-stimulating hormone), and their derivatives.

[0018] The polypetides used in the present invention include not only the naturally occurred polypeptides but also the physiologically active derivatives thereof. For instance, the calcitonins used in the present invention include not only the naturally occurred calcitonins such as salmon calcitonin, human calcitonin, porcine calcitonin, eel calcitonin, chicken calcitonin, rat calcitonin, bovine calcitonin, and sheep calcitonin, but also analogous products such as [$ASU^{1,7}$]-eel calcitonin, i.e. elcatonin.

[0019] The physiologically active polypeptides are contained in the composition in an amount sufficiently exhibiting the activities, which may vary depending on the kinds of the polypeptides. For instance, in case of calcitonins, the content thereof is in an amount wherein the calcitonins can sufficiently exhibit their activities suitable for treating paget's disease, hypercalcemia and osteoporosis.

[0020] The composition may optionally contain animal proteins and/or vegetable proteins in order to prevent any undesirable enzymolysis of the polypeptides during absorption after oral administration. The animal and vegetable proteins are preferably the conventional proteins suitable for foods and medicaments.

[0021] Preferred examples of the animal proteins are albumin (e.g. bovine serum albumin, human serum albumin, etc.), casein, gelatin, and the like. Preferred examples of the vegetable proteins are gluten, zein, soy bean protein, and the like. These animal and vegetable proteins may be used alone or in combination of an animal protein and a vegetable protein in an appropriate ratio. The amount of the animal and/or vegetable proteins to be incorporated into the composition may vary depending on the kinds of the polypeptides to be stabilized, but is usually in the range of 0.001 to 25 % by weight based on the whole weight of the composition.

[0022] The composition includes various types of composition, i.e. compositions for oral administration, such as tablets, capsules, granules, etc., and compositions for administration to the oral cavity, such as sublingual tablets. These compositions may be prepared in a conventional manner using the conventional carriers and diluents, such as excipients, binders, lubricants, etc.

[0023] The carriers used for tablets include excipients such as lactose, sucrose, glucose, starches, crystalline cellulose, etc. which are usually used in an amount of 50 to 90 % by weight based on the whole weight of the composition; binders such as hydroxypropyl cellulose, carboxymethyl cellulose, carboxymethyl cellulose sodium, gum arabic, gelatin, polyvinyl alcohol, polyvinylpyrrolidone, tragacanth, sodium arginate, etc. which are usually used in an amount of 1 to 25 % by weight based on the whole weight of the composition; lubricants such as magnesium stearate, calcium stearate, talc, etc. which are usually used in an amount of 0.5 to 3 % by weight based on the whole weight of the composition.

[0024] The materials for the enteric coating includes hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate phthalate, methacrylic copolymer, and the like.

[0025] The carriers used for sublingual tablets include excipients such as lactose, sucrose, mannitol, sorbitol, starches, etc. which are usually used in an amount of 50 to 90 % by weight based on the whole weight of the composition; binders such as crystalline cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, dextrin, etc. which are usually used in an amount of 1 to 15 % by weight based on the whole weight of the composition; disintegrators such as carboxymethyl cellulose calcium, low-substituted hydroxypropyl methyl cellulose, starches, etc. which are usually used in an amount of 1 to 15 % by weight based on the whole weight of the composition; lubricants such as magnesium stearate, calcium stearate, talc, etc. which are usually used in an amount of 0.5 to 3 % by weight based on the whole weight of the composition.

[0026] The composition for administration to the oral cavity, particularly sublingual tablets, include a rapidly soluble composition which is rapidly dissolved within the oral cavity. The rapidly soluble composition is prepared by using one or more of the carriers such as gelatin, agar, polyvinylpyrrolidone, or natural gums (e.g. guar gum, locust bean gum, etc.) instead of excipients, binders and lubricants, and mixing homogeneously the active polypeptides and the absorption promoting agents to the carriers and then lyophilizing the mixture in a conventional manner.

[0027] The present invention and the effects thereof are illustrated by the following Experiments and Examples.

Experiment 1

Effects for promoting absorption of calcitonin by a combination of various organic acids and various fatty acid sucrose esters:

[0028] Solutions containing bovine serum albumin (BSA) 0.3 w/v%, an absorption promoting agent (a combination of various organic acids 0.5 and 1.0 w/v% and sucrose laurate 0.5 w/v%) and human calcitonin (h-CT) 5 μg/ml were prepared.

[0029] Male Wistar rats (weighing about 250 g) were anestherized with Nembutal, and before administering the test solution (the calcitonin solution prepared above), the blood was collected from right external jugular vein. After subjecting the rats to ventrotomy, each calcitonin solution was administered to the lower part of the small intestine by a closed loop method in an amount of 0.1 ml per 100 g of rat. After the administration, the blood was collected at intervals (after 5, 15, 30 and 60 minutes). After the serum was separated, the calcium concentration in serum was measured with Calcium C kit (manufactured by Wako Junyaku K.K., Japan) (n = 3). The results are shown in Table 1.

Table 1

[Lowering rate of serum calcium (%)]					
Oragnic acids	Concentration (%)	Time after administration (min)			
		5	15	30	60
Malic acid	0.5	1.5	5.0	8.8	4.8
Succinic acid	0.5	2.6	4.7	3.9	-2.5
Lactic acid	0.5	1.9	7.6	9.0	4.4
Tartaric acid	0.5	3.9	5.3	5.2	-2.8
Tartaric acid	1.0	0.4	8.2	9.9	10.1
Citric acid	1.0	0.1	4.1	6.1	-2.8
Benzoic acid	1.0	2.9	10.8	10.1	8.3

[0030] As is shown in Table 1, in each test solution, the lowering of serum calcium was observed.

Experiment 2

Effects for promoting absorption of an active substance by using fatty acid sucrose esters having different HLB values:

[0031] Solutions containing BSA 0.3 w/v%, an absorption promoting agent (a combination of tartaric acid 1.0 w/v% and each of the following fatty acid sucrose esters 0.5 w/v%) and h-CT 10 μg/ml were prepared.

	Fatty acid sucrose esters	HLB value
1.	Sucrose stearate (S-270)	2
2.	" (S-970)	9
3.	" (S-1670)	16
4.	Sucrose laurate (L-1695)	16

[0032] As a reference solution, there was used a 0.1 M acetate buffer solution containing BSA 0.3 w/v%, tartaric acid 1.0 w/v% and h-CT 10 μg/ml.

[0033] In the same manner as described in Experiment 1, the test solution was administered, and the blood was collected at intervals (after 5, 15, 30 and 60 minutes). After the serum was separated, the h-CT concentration in serum was measured by RIA. The results are shown in the accompanying Fig. 1, wherein the value is shown by the difference to the initial value.

[0034] As is shown in Fig. 1, the calcitonin solutions of the invention showed the h-CT concentration in blood became maximum 5 minutes after the administration and showed higher h-CT concentration in blood than that of the reference solution (using tartaric acid alone).

Experiment 3

Effects for promoting absorption of an active substance by using fatty acid sucrose esters having different fatty acid residues:

[0035] By using fatty acid sucrose esters having HLB 16 and different fatty acid residues, there were prepared solutions containing BSA 0.3 w/v%, an absorption promoting agent (a combination of tartaric acid 1.0 w/v% and each of the following fatty acid sucrose esters 0.5 w/v%) and h-CT 5 μg/ml.

Fatty acid sucrose esters	Fatty acid residue
1. Sucrose stearate (S-1670)	stearic acid
2. Sucrose palmitate (S-1670)	palmitic acid
3. Sucrose laurate (L-1695)	lauric acid

[0036] In the same manner as described in Experiment 1, the test solution was administered to the rats, and the blood was collected at intervals and the calcium concentration in serum was measured likewise. The results are shown in the accompanying Fig. 2.

[0037] As is shown in Fig. 2, in all test solutions, there was observed lowering of blood calcium concentration while the fatty acid residue was different.

Experiment 4

Comparison of the effects for promoting absorption of an active substance between the use of tartaric acid or a fatty acid sucrose ester alone and the use of a combination thereof:

[0038] Solutions containing BSA 0.3 w/v%, an absorption promoting agent (a combination of tartaric acid 1.0 w/v% and sucrose laurate 0.5 w/v%) and h-CT 5 μg/ml and solutions containing BSA 0.3 w/v%, an absorption promoting agent (either alone of tartaric acid or sucrose laurate) and h-CT 5 μg/ml were prepared.

[0039] In the same manner as described in Experiment 1, the test solution was administered to the rats, and the blood was collected at intervals. After the serum was separated, the calcium concentration and h-CT concentration in serum were measured. The results are shown in the accompanying Fig. 3 and Fig. 4.

[0040] As are shown in Fig. 3 and Fig. 4, in view of the lowering of the blood calcium concentration and the change of the h-CT concentration in blood, the absorption promoting agent consisting of a combination of tartaric acid and sucrose laurate showed superior effects for promoting absorption of h-CT in comparison with the use of tartaric acid or sucrose laurate alone.

Experiment 5

Effects for promoting absorption of TSH:

[0041] A solution containing BSA 0.3 w/v%, an absorption promoting agent (a combination of tartaric acid 1.0 w/v% and sucrose stearate (S-1670) 0.5 w/v%) and TSH 500 μg/ml was prepared. As a reference solution, there was prepared a solution containing BSA 0.3 w/v% and TSH 500 μg/ml.

[0042] In the same manner as described in Experiment 1, the test solution was administered to the rats in an amount of TSH 100 μg per each rat and the blood was collected at intervals. After the serum was separated, the blood TSH concentration was measured by RIA. The results are shown in the accompanying Fig. 5.

[0043] As is shown in Fig. 5, the solution of the invention showed far higher increase of the blood TSH concentration than the reference solution containing no absorption promoting agent.

Experiment 6

Effects for promoting absorption of ACTH:

[0044] A solution containing BSA 0.3 w/v%, an absorption promoting agent (a combination of tartaric acid 1.0 w/v% and sucrose palmitate (P-1670) 0.5 w/v%) and ACTH 500 μg/ml was prepared. As a reference solution, there was prepared a solution containing BSA 0.3 w/v% and ACTH 500 μg/ml.

[0045] In the same manner as described in Experiment 1, the test solution was administered to the rats in an amount

of ACTH 100 μg per each rat and the blood was collected at intervals. After the serum was separated, the blood ACTH concentration was measured by RIA. The results are shown in the accompanying Fig. 6.

[0046] As is shown in Fig. 6, the solution using an absorption promoting agent of the invention showed far higher increase of the blood ACTH concentration than the reference solution containing no absorption promoting agent.

Example 1

Tablets:

[0047] In accordance with the tablet fomulation as shown in Table 2, lactose, corn starch, tartaric acid, a fatty acid sucrose ester (Ryoto Sugar Ester L-1695, manufactured by Mitsubishi Chemical, Japan), h-CT and BSA are mixed, and thereto is added an aqueous solution of hydroxypropyl cellulose (HPC). The mixture is kneaded and extrued to granulate to give granules. The granules are mixed with magnesium stearate, and the mixture is tableted with a tableting machine to give crude tablets (each diameter 8 mm, weight 250 mg).

Table 2

Tablet components	Amount
Lactose	22.8 g
Corn starch	21.0 g
Fatty acid sucrose ester	1.5 g
Tartaric acid	3.0 g
Human calcitonin (h-CT)	0.1 g
Bovine serum albumin (BSA)	0.3 g
Hydroxypropyl cellulose (HPC)	1.2 g
Magnesium stearate	0.1 g

[0048] The crude tablets thus prepared are coated with a coating liquid prepared according to the coating formulation as shown in Table 3 with a high coater to give the desired tablets.

Table 3

Coating formulation	Amount
Hydroxypropyl methyl cellulose acetate succinate	10 g
Triethyl citrate	2 g
Ethanol	80 g
Water	8 g

Example 2

Capsules:

[0049] In accordance with the capsule fomulation as shown in Table 4, malic acid, a fatty acid sucrose ester (Ryoto Sugar Ester L-1695, manufactured by Mitsubishi Chemical, Japan), salmon calcitonin and BSA are mixed, and the mixture (each 100 mg) is filled into Japan Pharmacopeia #4 capsule to give capsules.

Table 4

Capsule components	Amount
Malic acid	12.4 g
Fatty acid sucrose ester	6.0 g
Salmon calcitonin	0.4 g
Bovine serum albumin (BSA)	1.2 g

[0050] The capsules thus prepared are coated with a coating liquid prepared according to the coating formulation as shown in Table 5 with a fluidized granulator to give the desired capsules.

Table 5

Coating formulation	Amount
Methacrylic copolymer-S	20 g
Castor oil	3 g
Ethanol	377 g

Example 3

Granules:

[0051] In accordance with the granule fomulation as shown in Table 6, lactose, corn starch, human calcitonin, BSA, citric acid and a fatty acid sucrose ester are mixed, and thereto is added an aqueous solution of HPC. The mixture is kneaded and extrued to granulate to give granules.

Table 6

Granule components	Amount
Lactose	7.2 g
Corn starch	12.3 g
Human calcitonin	0.2 g
Bovine serum albumin (BSA)	0.6 g
Citric acid	6.2 g
Fatty acid sucrose ester	3.0 g
Hydroxypropyl cellulose (HPC)	0.5 g

[0052] The granules thus prepared are film-coated with a coating liquid prepared according to the coating formulation as shown in Table 7 with a fluidized granulator to give the desired granules.

Table 7

Coating formulation	Amount
Methacrylic copolymer-S	30 g
Castor Oil	1.5 g
Talc	15 g
Ethanol	498 g
Purified water	55.5 g

Example 4

Sublingual tablets:

[0053] In accordance with the fomulation as shown in Table 8, lactose, corn starch, hydroxypropyl cellulose, sucrose stearate, tartaric acid, and human calcitonin are mixed, and the mixture is tableted with a tableting machine to give the desired sublingual tablets.

Table 8

Sublingual tablet components	Amount
Lactose	75.6 g
Corn starch	13 g
Hydroxypropyl cellulose	1 g
Sucrose stearate	3 g
Tartaric acid	7 g
Human calcitonin (h-CT)	0.4 g

Example 5

Sublingual tablets:

[0054] In accordance with the fomulation as shown in Table 9, the desired sublingual tablets are prepared in the same manner as described in Example 4.

Table 9

Sublingual tablet components	Amount
Lactose	58.8 g
Crystalline cellulose	24 g
Polyvinylpyrrolidone	3 g
Sucrose palmitate	4 g
Malic acid	10 g
Human calcitonin (h-CT)	0.2 g

Example 6

Sublingual tablets:

[0055] In accordance with the fomulation as shown in Table 10, the desired sublingual tablets are prepared in the same manner as described in Example 4.

Table 10

Sublingual tablet components	Amount
Lactose	67 g
Sorbitol	4 g
Mannitol	8.4 g
Carboxymethyl cellulose sodium	2.6 g
Sucrose oleate	5 g
Citric acid	12 g
Salmon calcitonin	1 g

Experiment 7

Effects for promoting absorption of calcitonin in sublingual tablets:

[0056] The sublingual tablets prepared as in Examples 4 and 5 were used as the test material (content of calcitonin, 1 mg or 0.5 mg per each tablet, 250 mg).

[0057] The test material (each one tablet) was administered by a sublingual route to a male Beagle dog which fasted overnight. After the administration, the blood was collected at intervals (after 5, 10, 15, 20, 30, 45, 60 and 120 minutes). After the serum was separated, the blood human calcitonin concentration was measured by RIA. The results are shown in the accompanying Fig. 7.

Example 7

Rapidly soluble preparation:

[0058] In accordance with the fomulation as shown in Table 11, salmon calcitonin 10 mg, tartaric acid 2 g, and sucrose stearate 1 g are dissolved in an aqueous gelatin solution (1 w/v%) 10 ml. The solution (each 1 ml) is added to a vessel, followed by lyophilization to give the desired rapidly soluble preparation (sublingual tablets).

Table 11

Raidly soluble prepar. components	Amount
Aqueous gelatin solution (1 w/v%)	10 ml
Tartaric acid	2g
Sucrose stearate	1g
Salmon calcitonin	10g

Example 8

Rapidly soluble preparation:

[0059] In accordance with the fomulation as shown in Table 12, the desired rapidly soluble preparation (sublingual tablets) is prepared in the same manner as described in Example 7.

Table 12

Raidly soluble prepar. components	Amount
Aqueous gelatin solution (1 w/v%)	10 ml
Citric acid	1 g
Sucrose oleate	0.2 g
Human calcitonin	10 mg

Experiment 8

Effects for promoting absorption of calcitonin by using a combination of various organic acids and a fatty acid sucrose ester in rapidly soluble composition:

[0060] Test materials were prepared by dissolving salmon calcitonin 3 mg, an organic acid 20 w/v%, and sucrose stearate (S-970) 10 w/v% to a 1 w/v% aqueous gelatin solution 3 ml, adding the solution (each 1 ml) to a vessel, followed by lyophilization.

[0061] Each one of the test material was administered by a sublingual route to a male Beagle dog which fasted overnight, and the blood was collected at intervals (after 10, 20, 30, 45 and 60 minutes). After the serum was separated, the calcium concentration in serum was measured with Calcium C kit (manufactured by Wako Junyaku K.K., Japan) (n = 3). The results are shown in Table 13.

[0062] As is shown in Table 13, in each material using any organic acid, there was observed the lowering of blood calcium concentration, while no lowering of blood calcium concentration was observed in the material using no organic acid.

Table 13

[Lowering rate of serum calcium (%)]					
Oragnic acids	Time after administration (min)				
	10	20	30	45	60
Tartaric acid	3.0	2.9	5.1	8.3	7.8
Citric acid	4.5	2.3	3.0	1.6	2.2
Malic acid	4.5	2.7	3.3	1.4	1.5
(-)	-2.2	-1.5	-3.6	-3.1	-4.1

Experiment 9

Effects for promoting absorption of an active substance by using fatty acid sucrose esters having different HLB values in rapidly soluble composition:

[0063] Test materials were prepared by dissolving salmon calcitonin 3 mg, tartaric acid 20 w/v%, and each fatty acid

sucrose ester 10 w/v% to a 1 w/v% aqueous gelatin solution 3 ml, adding the solution (each 1 ml) to a vessel, followed by lyophilization.

[0064] In the same manner as described in Experiment 8, the test material was administered to the dog, and the blood was collected at intervals, and the blood calcium concentration was measured. The results are shown in Table 14.

[0065] As is shown in Table 14, in each material using fatty acid sucrose esters having various HLB values, there was observed the lowering of blood calcium concentration.

Table 14

[Lowering rate of serum calcium (%)]					
HLB values	Time after administration (min)				
	10	20	30	45	60
9	3.0	2.9	5.1	8.3	7.8
5	3.0	7.5	4.1	8.6	6.1
3	4.7	3.3	3.2	2.8	3.6

Experiment 10

Effects of the concentration of an organic acid and a fatty acid sucrose ester on the absorption of the active ingredient in rapidly soluble composition:

[0066] Test materials were prepared by dissolving human calcitonin 3 mg, citric acid and sucrose stearate (S-970) in the concentration as shown in Table 15 to a 1 w/v% aqueous gelatin solution 3 ml, adding the solution (each 1 ml) to a vessel, followed by lyophilization.

[0067] In the same manner as in Experiment 8, the test material was administered to the dog, and the blood was collected at intervals. After the serum was separated, the human calcitonin concentration in serum was measured by RIA. The results are shown in Table 15.

[0068] As is shown in Table 15, in the test materials of all concentrations of the organic acid and fatty acid sucrose ester, there was observed the absorption of human calcitonin, but the absorption promoting effect became weaker with lowering of the concentration of the absorption promoting agent.

Table 15

Concentration of absorption promoting agents (w/v%)		Maximum blood concentration of human calcitonin in average (pg/ml)
S-970	Citric acid	
10.0	20.0	1652
5.0	10.0	1116
2.5	5.0	191
1.0	2.0	86

Experiment 11

Effects for promoting absorption of calcitonin by using a combination of an organic acid and a fatty acid sucrose ester in rapidly soluble composition:

[0069] Test materials were prepared by dissolving human calcitonin (h-CT) 3 mg, tartaric acid 10 w/v%, and sucrose stearate (S-570) 2 w/v% to a 1 w/v% aqueous gelatin solution 3 ml, adding the solution (each 1 ml) to a vessel, followed by lyophilization.

[0070] In the same manner as described in Experiment 8, the test material was administered to the dog, and the blood was collected at intervals. After the serum was separated, there were measured the blood calcium concentration with Calcium C kit (manufactured by Wako Junyaku K.K., Japan), the blood phosphur concentration with Phosphur-C Test (manufactured by Wako Junyaku K.K., Japan), and the blood human calcitonin concentration by RIA. The results are shown in the accompanying Fig. 8.

[0071] As is shown in Fig. 8, with increase of the blood human calcitonin, the concentrations of calcium and phosphur in blood were lowered.

Effects of the Invention

[0072] When polypeptide hormones are administered orally, they are usually decomposed by a protease and hence are insufficiently absorbed and can not exhibit their sufficient physiological activities. From this viewpoint, the polypeptide hormones are usually administered by injection. On the contrary, according to the present invention, due to the use of an absorption promoting agent the polypeptide hormones can highly be absorbed through the intestinal tract and the membrane within the oral cavity, and thereby, the hormones can exhibit their physiological activities even by oral administration or by administration into the oral cavity.

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, MC, NC, PT, SE

1. Use of an absorption promoting agent consisting of an organic acid and a fatty acid sucrose ester for the preparation of a pharmaceutical composition for oral administration or for administration to the oral cavity which comprises a physiologically active polypeptide as an active ingredient.

2. The use according to claim 1, wherein the organic acid is a member selected from the group consisting of acetic acid, butyric acid, fumaric acid, malonic acid, phthalic acid, propionic acid, glutaric acid, adipic acid, valeric acid, caproic acid, maleic acid, ascorbic acid, isoascorbic acid, malic acid, succinic acid, lactic acid, tartaric acid, citric acid and benzoic acid, and the fatty acid sucrose ester is a member selected from the group consisting of sucrose stearate, sucrose palmitate, sucrose oleate, sucrose laureate, sucrose behenate and sucrose erucate.

3. The use according to claim 1, wherein the peptide is a member selected from the group consisting of insulin, angiotensin, vasopressin, desmopressin, LH-RH (luteinizing hormone-releasing hormone), somatostatin, calcitonin, glucagon, oxytocin, gastrins, somatomedins, secretin, h-ANP (human atrial natriuretic peptide or factor), ACTH (adrenocortico-tropic hormone), MSH (melanocyte-stimulating hormone), β-endorphin, muramyl dipeptide, enkephalins, neurotensin, bombesin, VIP (vaso-acrive intestinal polypeptide), CCK-8 (cholecystokin-8), PTH (parathyroid hormone), CGRP (calcitonin gene related peptide), TRH (thyrotropin releasing hormone), endothelin, TSH (thyroid-stimulating hormone) and their derivatives.

4. Use of an absorption promoting agent consisting of an organic acid and a fatty acid sucrose ester for the preparation of a pharmaceutical composition for oral administration or for administration to the oral cavity which comprises an effective amount of a physiologically active polypeptide in admixture with a pharmaceutically acceptable carrier or diluent,

   wherein said physiologically active peptide is a member selected from the group consisting of insulin, angiotensin, vasopressin, desmopressin, LH-RH (luteinizing hormone-releasing hormone), somatostatin, calcitonin, glucagon, oxytocin, gastrins, somatomedins, secretin, h-ANP (human atrial natriuretic peptide or factor), ACTH (adrenocortico-tropic hormone), MSH (melanocyte-stimulating hormone), β-endorphin, muramyl dipeptide, enkephalins, neurotensin, bombesin, VIP (vaso-active intestinal polypeptide), CCK-8 (cholecystokin-8), PTH (parathyroid hormone), CGRP (calcitonin gene related peptide), TRH (thyrotropin releasing hormone), endothelin, TSH (thyroid-stimulating hormone) and their derivatives;

   wherein said organic acid is a member selected from the group consisting of acetic acid, butyric acid, fumaric acid, malonic acid, phthalic acid, propionic acid, glutaric acid, adipic acid, valeric acid, caproic acid, maleic acid, ascorbic acid, isoascorbic acid, malic acid, succinic acid, lactic acid, tartaric acid, citric acid, and benzoic acid, and a combination of one or more thereof;

   wherein said fatty acid sucrose ester is a member selected from the group consisting of sucrose.stearate, sucrose palmitate, sucrose oleate, sucrose laureate, sucrose behenate, and sucrose erucate and a combination of one or more thereof ; and

   wherein said organic acid is present in an amount of 0.1 to 70% by weight based on the whole amount of the composition, and said fatty acid sucrose ester is present in an amount of 0.1 to 50% by weight based on the whole amount of the composition when the composition is in the form of oral administration, or

   said organic acid is present in an amount of 0.1 to 30% by weight based on the whole amount of the composition, and said fatty acid sucrose ester is present.in an amount of 0.1 to 20% by weight based on the whole amount of the composition when the composition is in the form of a composition for oral administration or for administration to the oral cavity or

said organic acid is present in an amount of 30 to 90% by weight based on the whole amount of the composition, and said fatty acid sucrose ester is present in an amount of to 50% by weight based on the whole amount of the composition when the composition is in the form of a rapidly soluble composition for administration to the oral cavity.

5. The use according to claim 4, wherein the calcitonin is [ASU^{1,7}] -eel calcitonin.

6. The use according to claim 4, wherein the composition is a composition for oral administration.

7. The use according to claim 4, wherein the composition is a composition for sublingual administration.

8. The use according to claim 7, wherein the composition is a rapidly soluble composition.

Claims for the following Contracting States : ES, GR

1. Use of an absorption promoting agent consisting of an organic acid and a fatty acid sucrose ester for a process for the preparation of a pharmaceutical composition for oral administration or for administration to the oral cavity which comprises a physiologically active polypeptide as an active ingredient.

2. The use according to claim 1, wherein the: organic acid is a member selected from the group consisting of acetic acid, butyric acid, fumaric acid, malonic acid, phthalic acid, propionic acid, glutaric acid, adipic acid, valeric acid, caproic acid, maleic acid, ascorbic acid, isoascorbic acid, malic acid, succinic acid, lactic acid, tartaric acid, citric acid and benzoic acid, and the fatty acid sucrose ester is a member selected from the group consisting of sucrose stearate, sucrose palmitate, sucrose oleate, sucrose laureate, sucrose behenate and sucrose erucate.

3. The use according to claim 1, wherein the peptide is a member selected from the group consisting of insulin, angiotensin, vasopressin, desmopressin, LH-RH (luteinizing hormone-releasing hormone), somatostatin, calcitonin, glucagon, oxytocin, gastrins, somatomedins, secretin, h-ANP (human atrial natriuretic peptide or factor), ACTH (adreno-cortico-tropic hormone), MSH (melanocyte-stimulating hormone), β-endorphin, muramyl dipeptide, enkephalins, neurotensin, bombesin, VIP (vaso-active intestinal polypeptide), CCK-8 (cholecystokin-8), PTH (parathyroid hormone), CGRP (calcitonin gene related peptide), TRH (thyrotropin releasing hormone), endothelin, TSH (thyroid-stimulating hormone) and their derivatives.

4. Use of an absorption promoting agent consisting of an organic acid and a fatty acid sucrose ester for the process for the preparation of a pharmaceutical composition for oral administration or for administration to the oral cavity which comprises an effective amount of a physiologically active polypeptide in admixture with a pharmaceutically acceptable carrier or diluent,

wherein said physiologically active peptide is a member selected from the group consisting of insulin, angiotensin, vasopressin, desmopressin, LH-RH (luteinizing hormone-releasing hormone), somatostatin, calcitonin, glucagon, oxytocin, gastrins, somatomedins, secretin, h-ANP (human atrial natriuretic peptide or factor), ACTH (adrenocortico-tropic hormone), MSH (melanocyte-stimulating hormone), β-endorphin, muramyl dipeptide, enkephalins, neurotensin, bombesin, VIP (vaso-active intestinal polypeptide), CCK-8 (cholecystokin-8), PTH (parathyroid hormone), CGRP (calcitonin gene related peptide), TRH (thyrotropin releasing hormone), endothelin, TSH (thyroid-stimulating hormone) and their derivatives;

wherein said organic acid is a member selected from the group consisting of acetic acid, butyric acid, fumaric acid, malonic acid, phthalic acid, propionic acid, glutaric acid, adipic acid, valeric acid, caproic acid, maleic acid, ascorbic acid, isoascorbic acid, malic acid, succinic acid, lactic acid, tartaric acid, citric acid and benzoic acid, and a combination of one or more thereof;

wherein said fatty acid sucrose ester is a member selected from the group consisting of sucrose.stearate, sucrose palmitate, sucrose oleate, sucrose laureate, sucrose behenate, and sucrose erucate and a combination of one or more thereof; and

wherein said organic acid is present in an amount of 0.1 to 70% by weight based on the whole amount of the composition, and said fatty acid sucrose ester is present in an amount of 0.1 to 50% by weight based on the whole amount of the composition when the composition is in the form of oral administration, or

said organic acid is present in an amount of 0.1 to 30% by weight based on the whole amount of the composition, and said fatty acid sucrose ester is present in an amount of 0.1 to 20% by weight based on the whole amount of the composition when the composition is in the form of a composition for administration to the oral cavity

or

said organic acid is present in an amount of 30 to 90% by weight based on the whole amount of the composition, and said fatty acid sucrose ester is present in an amount of 5 to 50% by weight based on the whole amount of the composition when the composition is in the form of a rapidly soluble composition for administration to the oral cavity.

5. The use according to claim 4, wherein the calcitonin is [ASU^{1,7}]-eel calcitonin.

6. The use according to claim 4, wherein the composition is a composition for oral administration.

7. The use according to claim 4, wherein the composition is a composition for sublingual administration.

8. The use according to claim 7, wherein the composition is a rapidly soluble composition.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, MC, NL, PT, SE:

1. Verwendung eines die Absorption fördernden Mittels, das aus einer organischen Säure und einem Fettsäuresaccharoseester besteht, für die Herstellung einer pharmazeutischen Zusammensetzung zur oralen Verabreichung oder zur Verabreichung in die Mundhöhle, die ein physiologisch aktives Polypeptid als Wirkstoff umfasst.

2. Verwendung nach Anspruch 1, wobei die organische Säure ein Glied, ausgewählt aus der Gruppe, bestehend aus Essigsäure, Buttersäure, Fumarsäure, Malonsäure, Phthalsäure, Propionsäure, Glutarsäure, Adipinsäure, Valeriansäure, Capronsäure, Maleinsäure, Ascorbinsäure, Isoascorbinsäure, Äpfelsäure, Bernsteinsäure, Milchsäure, Weinsäure, Zitronensäure und Benzoesäure, ist und der Fettsäuresaccharoseester ein Glied, ausgewählt aus der Gruppe, bestehend aus Saccharosestearat, Saccharosepalmitat, Saccharoseoleat, Saccharoselaureat, Saccharosebehenat und Saccharoseerucat, ist.

3. Verwendung nach Anspruch 1, wobei das Peptid ein Glied, ausgewählt aus der Gruppe, bestehend aus Insulin, Angiotensin, Vasopressin, Desmopressin, LH-RH (Luteinisierungshormon freisetzendes Hormon), Somatostatin, Calcitonin, Glucagon, Oxytocin, Gastrinen, Somatomedinen, Secretin, h-ANP (humanes natriuretisches Atriumpeptid oder humaner natriuretischer Atriumfaktor), ACTH (adreno-kortikotropes Hormon), MSH (Melanozyten-stimulierendes Hormon), β-Endorphin, Muramyldipeptid, Enkephalinen, Neurotensin, Bombesin, VIP (vasoaktives intestinales Polypeptid), CCK-8 (Cholecystokin-8), PTH (Parathormon), CGRP (calcitonin gene related peptide), TRH (Thyreotropin-releasing-Hormon), Endothelin, TSH (Thyreotropin) und deren Derivaten, ist.

4. Verwendung eines die Absorption fördernden Mittels, das aus einer organischen Säure und einem Fettsäuresaccharoseester besteht, für die Herstellung einer pharmazeutischen Zusammensetzung zur oralen Verabreichung oder zur Verabreichung in die Mundhöhle, die eine wirksame Menge eines physiologisch aktiven Polypeptids im Gemisch mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel umfasst,
wobei das physiologisch aktive Peptid ein Glied, ausgewählt aus der Gruppe, bestehend aus Insulin, Angiotensin, Vasopressin, Desmopressin, LH-RH (Luteinisierungshormon freisetzendes Hormon), Somatostatin, Calcitonin, Glucagon, Oxytocin, Gastrinen, Somatomedinen, Secretin, h-ANP (humanes natriuretisches Atriumpeptid oder humaner natriuretischer Atriumfaktor), ACTH (adreno-korticotropes Hormon), MSH (Melanocytenstimulierendes Hormon), β-Endorphin, Muramyldipeptid, Enkephalinen, Neurotensin, Bombesin, VIP (vasoaktives intestinales Polypeptid), CCK-8 (Cholecystokin-8), PTH (Parathormon), CGRP (calcitonin gene related peptide), TRH (Thyreotropin-releasing-Hormon), Endothelin, TSH (Thyreotropin) und deren Derivaten, ist;
wobei die organische Säure ein Glied, ausgewählt aus der Gruppe, bestehend aus Essigsäure, Buttersäure, Fumarsäure, Malonsäure, Phthalsäure, Propionsäure, Glutarsäure, Adipinsäure, Valeriansäure, Capronsäure, Maleinsäure, Ascorbinsäure, Isoascorbinsäure, Äpfelsäure, Bernsteinsäure, Milchsäure, Weinsäure, Zitronensäure und Benzoesäure und einer Kombination aus einem oder mehreren davon, ist;
wobei der Fettsäuresaccharoseester ein Glied, ausgewählt aus der Gruppe, bestehend aus Saccharosestearat, Saccharosepalmitat, Saccharoseoleat, Saccharoselaureat, Saccharosebehenat und Saccharoseerucat und einer Kombination aus einem oder mehreren davon, ist und
wobei die organische Säure in einer Menge von 0,1 bis 70 Gew.-%, bezogen auf die Gesamtmenge der Zusam-

mensetzung, vorhanden ist und der Fettsäuresaccharoseester in einer Menge von 0,1 bis 50 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung, vorhanden ist, wenn die Zusammensetzung in einer Form zur oralen Verabreichung ist, oder
die organische Säure in einer Menge von 0,1 bis 30 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung, vorliegt und der Fettsäuresaccharoseester in einer Menge von 0,1 bis 20 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung, vorliegt, wenn die Zusammensetzung in Form einer Zusammensetzung zur oralen Verabreichung oder zur Verabreichung in die Mundhöhle vorliegt, oder
die organische Säure in einer Menge von 30 bis 90 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung vorliegt, und der Fettsäuresaccharoseester in einer Menge von 5 bis 50 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung vorliegt, wenn die Zusammensetzung in Form einer schnell löslichen Zusammensetzung zur Verabreichung in die Mundhöhle vorliegt.

5. Verwendung nach Anspruch 4, wobei das Calcitonin [ASU^{1,7}]-eel-Calcitonin ist.

6. Verwendung nach Anspruch 4, wobei die Zusammensetzung eine Zusammensetzung zur oralen Verabreichung ist.

7. Verwendung nach Anspruch 4, wobei die Zusammensetzung eine Zusammensetzung zur sublingualen Verabreichung ist.

8. Verwendung nach Anspruch 7, wobei die Zusammensetzung eine schnell lösliche Zusammensetzung ist.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verwendung eines die Absorption fördernden Mittels, das aus einer organischen Säure und einem Fettsäuresaccharoseester besteht, für ein Verfahren für die Herstellung einer pharmazeutischen Zusammensetzung zur oralen Verabreichung oder zur Verabreichung in die Mundhöhle, die ein physiologisch aktives Polypeptid als Wirkstoff umfasst.

2. Verwendung nach Anspruch 1, wobei die organische Säure ein Glied, ausgewählt aus der Gruppe, bestehend aus Essigsäure, Buttersäure, Fumarsäure, Malonsäure, Phthalsäure, Propionsäure, Glutarsäure, Adipinsäure, Valeriansäure, Capronsäure, Maleinsäure, Ascorbinsäure, Isoascorbinsäure, Äpfelsäure, Bernsteinsäure, Milchsäure, Weinsäure, Zitronensäure und Benzoesäure, ist und der Fettsäuresaccharoseester ein Glied, ausgewählt aus der Gruppe, bestehend aus Saccharosestearat, Saccharosepalmitat, Saccharoseoleat, Saccharoselaureat, Saccharosebehenat und Saccharoseerucat, ist.

3. Verwendung nach Anspruch 1, wobei das Peptid ein Glied, ausgewählt aus der Gruppe, bestehend aus Insulin, Angiotensin, Vasopressin, Desmopressin, LH-RH (Luteinisierungshormon freisetzendes Hormon), Somatostatin, Calcitonin, Glucagon, Oxytocin, Gastrinen, Somatomedinen, Secretin, h-ANP (humanes natriuretisches Atriumpeptid oder humaner natriuretischer Atriumfaktor), ACTH (adreno-kortikotropes Hormon), MSH (Melanozyten-stimulierendes Hormon), β-Endorphin, Muramyldipeptid, Enkephalinen, Neurotensin, Bombesin, VIP (vasoaktives intestinales Polypeptid), CCK-8 (Cholecystokin-8), PTH (Parathormon), CGRP (calcitonin gene related peptide), TRH (Thyreotropin-releasing-Hormon), Endothelin, TSH (Thyreotropin) und deren Derivaten, ist.

4. Verwendung eines die Absorption fördernden Mittels, dass aus einer organischen Säure und einem Fettsäuresaccharoseester besteht, für ein Verfahren für die Herstellung einer pharmazeutischen Zusammensetzung zur oralen Verabreichung oder zur Verabreichung in die Mundhöhle, die eine wirksame Menge eines physiologisch aktiven Polypeptids im Gemisch mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel umfasst,
wobei das physiologisch aktive Peptid ein Glied, ausgewählt aus der Gruppe bestehend aus Insulin, Angiotensin, Vasopressin, Desmopressin, LH-RH (Luteinisierungshormon freisetzendes Hormon), Somatostatin, Calcitonin, Glucagon, Oxytocin, Gastrinen, Somatomedinen, Secretin, h-ANP (humanes natriuretisches Atriumpeptid oder humaner natriuretischer Atriumfaktor), ACTH (adreno-korticotropes Hormon), MSH (Melanocytenstimulierendes Hormon), β-Endorphin, Muramyldipeptid, Enkephalinen, Neurotensin, Bombesin, VIP (vasoaktives intestinales Polypeptid), CCK-8 (Cholecystokin-8), PTH (Parathormon), CGRP (calcitonin gene related peptide), TRH (Thyreotropin-releasing-Hormon), Endothelin, TSH (Thyreotropin) und deren Derivaten, ist;
wobei die organische Säure ein Glied, ausgewählt aus der Gruppe, bestehend aus Essigsäure, Buttersäure, Fumarsäure, Malonsäure, Phthalsäure, Propionsäure, Glutarsäure, Adipinsäure, Valeriansäure, Capronsäure, Maleinsäure, Ascorbinsäure, Isoascorbinsäure, Äpfelsäure, Bernsteinsäure, Milchsäure, Weinsäure, Zitronensäure

und Benzoesäure und einer Kombination aus einem oder mehreren davon, ist;
wobei der Fettsäuresaccharoseester ein Glied, ausgewählt aus der Gruppe, bestehend aus Saccharosestearat, Saccharosepalmitat, Saccharoseoleat, Saccharoselaureat, Saccharosebehenat und Saccharoseerucat und einer Kombination aus einem oder mehreren davon, ist und
wobei die organische Säure in einer Menge von 0,1 bis 70 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung, vorhanden ist und der Fettsäuresaccharoseester in einer Menge von 0,1 bis 50 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung, vorhanden ist, wenn die Zusammensetzung in einer Form zur oralen Verabreichung ist, oder
die organische Säure in einer Menge von 0,1 bis 30 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung, vorliegt und der Fettsäuresaccharoseester in einer Menge von 0,1 bis 20 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung, vorliegt, wenn die Zusammensetzung in Form einer Zusammensetzung zur Verabreichung in die Mundhöhle vorliegt, oder
die organische Säure in einer Menge von 30 bis 90 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung vorliegt, und der Fettsäuresaccharoseester in einer Menge von 5 bis 50 Gew.-%, bezogen auf die Gesamtmenge der Zusammensetzung vorliegt, wenn die Zusammensetzung in Form einer schnell löslichen Zusammensetzung zur Verabreichung in die Mundhöhle vorliegt.

5. Verwendung nach Anspruch 4, wobei das Calcitonin [ASU^{1,7}]-eel-Calcitonin ist.

6. Verwendung nach Anspruch 4, wobei die Zusammensetzung eine Zusammensetzung zur oralen Verabreichung ist.

7. Verwendung nach Anspruch 4, wobei die Zusammensetzung eine Zusammensetzung zur sublingualen Verabreichung ist.

8. Verwendung nach Anspruch 7, wobei die Zusammensetzung eine schnell lösliche Zusammensetzung ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, MC, NL, PT, SE

1. Utilisation d'un agent favorisant l'absorption consistant en un acide organique et un ester d'acide gras et de saccharose pour la préparation d'une composition pharmaceutique pour l'administration orale
ou pour l'administration à la cavité orale qui comprend un polypeptide physiologiquement actif comme ingrédient actif.

2. Utilisation selon la revendication 1 où l'acide organique est un membre choisi dans le groupe consistant en l'acide acétique, l'acide butyrique, l'acide fumarique, l'acide malonique, l'acide phtalique, l'acide propionique, l'acide glutarique, l'acide adipique, l'acide valérique, l'acide caproïque, l'acide maléique, l'acide ascorbique, l'acide isoascorbique, l'acide malique, l'acide succinique, l'acide lactique, l'acide tartrique, l'acide citrique et l'acide benzoïque, et l'ester d'acide gras et de saccharose est un membre choisi dans le groupe consistant en le stéarate de saccharose, le palmitate de saccharose, l'oléate de saccharose, le laurate de saccharose, le béhénate de saccharose et l'érucate de saccharose.

3. Utilisation selon la revendication 1 où le peptide est un membre choisi dans le groupe consistant en l'insuline, l'angiotensine, la vasopressine, la desmopressine, LH-RH (hormone libérant la lutéinostimuline), la somatostatine, la calcitonine, le glucagon, l'oxytocine, les gastrines, les somatomédines, la sécrétine, h-ANP (peptide ou facteur natriurétique auriculaire humain), ACTH (hormone adrénocorticotrope), MSH (hormone mélanostimulante), la β-endorphine, le muramyldipeptide, les enképhalines, la neurotensine, la bombésine, VIP (polypeptide intestinal vasoactif), CCK-8 (cholécystokine-8), PTH (hormone parathyroïdienne), CGRP (peptide apparenté au gène de calcitonine), TRH (hormone libérant la thyréostimuline), l'endothéline, TSH (thyréostimuline) et leurs dérivés.

4. Utilisation d'un agent favorisant l'absorption consistant en un acide organique et un ester d'acide gras et de saccharose pour la préparation d'une composition pharmaceutique pour l'administration orale
ou pour l'administration à la cavité orale qui comprend une quantité efficace d'un polypeptide physiologiquement actif en mélange avec un support ou diluant pharmaceutiquement acceptable,
où ledit peptide physiologiquement actif est un membre choisi dans le groupe consistant en l'insuline, l'angioten-

sine, la vasopressine, la desmopressine, LH-RH (hormone libérant la lutéinostimuline), la somatostatine, la calcitonine, le glucagon, l'oxytocine, les gastrines, les somatomédines, la sécrétine, h-ANP (peptide ou facteur natriurétique auriculaire humain), ACTH (hormone adrénocorticotrope), MSH (hormone mélanostimulante), la β-endorphine, le muramyldipeptide, les enképhalines, la neurotensine, la bombésine, VIP (polypeptide intestinal vasoactif), CCK-8 (cholécystokine-8), PTH (hormone parathyroïdienne), CGRP (peptide apparenté au gène de calcitonine), TRH (hormone libérant la thyréostimuline), l'endothéline, TSH (thyréostimuline) et leurs dérivés ;
où ledit acide organique est un membre choisi dans le groupe consistant en l'acide acétique, l'acide butyrique, l'acide fumarique, l'acide malonique, l'acide phtalique, l'acide propionique, l'acide glutarique, l'acide adipique, l'acide valérique, l'acide caproïque, l'acide maléique, l'acide ascorbique, l'acide isoascorbique, l'acide malique, l'acide succinique, l'acide lactique, l'acide tartrique, l'acide citrique et l'acide benzoïque, et une combinaison d'un ou plusieurs d'entre eux ;
où ledit ester d'acide gras et de saccharose est un membre choisi dans le groupe consistant en le stéarate de saccharose, le palmitate de saccharose, l'oléate de saccharose, le laurate de saccharose, le béhénate de saccharose et l'érucate de saccharose et une combinaison d'un ou plusieurs d'entre eux ; et
où ledit acide organique est présent en une quantité de 0,1 à 70 % en masse sur la base de la quantité totale de la composition, et ledit ester d'acide gras et de saccharose est présent en une quantité de 0,1 à 50 % en masse sur la base de la quantité totale de la composition quand la composition est sous la forme d'administration orale, ou ledit acide organique est présent en une quantité de 0,1 à 30 % en masse sur la base de la quantité totale de la composition, et ledit ester d'acide gras et de saccharose est présent en une quantité de 0,1 à 20 % en masse sur la base de la quantité totale de la composition quand la composition est sous la forme d'une composition pour l'administration orale ou pour l'administration à la cavité orale ou
ledit acide organique est présent en une quantité de 30 à 90 % en masse sur la base de la quantité totale de la composition, et ledit ester d'acide gras et de saccharose est présent en une quantité de 5 à 50 % en masse sur la base de la quantité totale de la composition quand la composition est sous la forme d'une composition rapidement soluble pour l'administration à la cavité orale.

5. Utilisation selon la revendication 4 où la calcitonine est la calcitonine d'anguille [ASU^{1,7}].

6. Utilisation selon la revendication 4 où la composition est une composition pour l'administration orale.

7. Utilisation selon la revendication 4 où la composition est une composition pour l'administration sublinguale.

8. Utilisation selon la revendication 7 où la composition est une composition rapidement soluble.

Revendications pour les Etats contractants suivants : ES, GR

1. Utilisation d'un agent favorisant l'absorption consistant en un acide organique et un ester d'acide gras et de saccharose pour un procédé pour la préparation d'une composition pharmaceutique pour l'administration orale ou pour l'administration à la cavité orale qui comprend un polypeptide physiologiquement actif comme ingrédient actif.

2. Utilisation selon la revendication 1 où l'acide organique est un membre choisi dans le groupe consistant en l'acide acétique, l'acide butyrique, l'acide fumarique, l'acide malonique, l'acide phtalique, l'acide propionique, l'acide glutarique, l'acide adipique, l'acide valérique, l'acide caproïque, l'acide maléique, l'acide ascorbique, l'acide isoascorbique, l'acide malique, l'acide succinique, l'acide lactique, l'acide tartrique, l'acide citrique et l'acide benzoïque, et l'ester d'acide gras et de saccharose est un membre choisi dans le groupe consistant en le stéarate de saccharose, le palmitate de saccharose, l'oléate de saccharose, le laurate de saccharose, le béhénate de saccharose et l'érucate de saccharose.

3. Utilisation selon la revendication 1 où le peptide est un membre choisi dans le groupe consistant en l'insuline, l'angiotensine, la vasopressine, la desmopressine, LH-RH (hormone libérant la lutéinostimuline), la somatostatine, la calcitonine, le glucagon, l'oxytocine, les gastrines, les somatomédines, la sécrétine, h-ANP (peptide ou facteur natriurétique auriculaire humain), ACTH (hormone adrénocorticotrope), MSH (hormone mélanostimulante), la β-endorphine, le muramyldipeptide, les enképhalines, la neurotensine, la bombésine, VIP (polypeptide intestinal vasoactif), CCK-8 (cholécystokine-8), PTH (hormone parathyroïdienne), CGRP (peptide apparenté au gène de calcitonine), TRH (hormone libérant la thyréostimuline), l'endothéline, TSH (thyréostimuline) et leurs dérivés.

4. Utilisation d'un agent favorisant l'absorption consistant en un acide organique et un ester d'acide gras et de sac-

charose pour le procédé pour la préparation d'une composition pharmaceutique pour l'administration orale ou pour l'administration à la cavité orale qui comprend une quantité efficace d'un polypeptide physiologiquement actif en mélange avec un support ou diluant pharmaceutiquement acceptable,
où ledit peptide physiologiquement actif est un membre choisi dans le groupe consistant en l'insuline, l'angiotensine, la vasopressine, la desmopressine, LH-RH (hormone libérant la lutéinostimuline), la somatostatine, la calcitonine, le glucagon, l'oxytocine, les gastrines, les somatomédines, la sécrétine, h-ANP (peptide ou facteur natriurétique auriculaire humain), ACTH (hormone adrénocorticotrope), MSH (hormone mélanostimulante), la β-endorphine, le muramyldipeptide, les enképhalines, la neurotensine, la bombésine, VIP (polypeptide intestinal vasoactif), CCK-8 (cholécystokine-8), PTH (hormone parathyroïdienne), CGRP (peptide apparenté au gène de calcitonine), TRH (hormone libérant la thyréostimuline), l'endothéline, TSH (thyréostimuline) et leurs dérivés ;
où ledit acide organique est un membre choisi dans le groupe consistant en l'acide acétique, l'acide butyrique, l'acide fumarique, l'acide malonique, l'acide phtalique, l'acide propionique, l'acide glutarique, l'acide adipique, l'acide valérique, l'acide caproïque, l'acide maléique, l'acide ascorbique, l'acide isoascorbique, l'acide malique, l'acide succinique, l'acide lactique, l'acide tartrique, l'acide citrique et l'acide benzoïque, et une combinaison d'un ou plusieurs d'entre eux ;
où ledit ester d'acide gras et de saccharose est un membre choisi dans le groupe consistant en le stéarate de saccharose, le palmitate de saccharose, l'oléate de saccharose, le laurate de saccharose, le béhénate de saccharose et l'érucate de saccharose et une combinaison d'un ou plusieurs d'entre eux ; et
où ledit acide organique est présent en une quantité de 0,1 à 70 % en masse sur la base de la quantité totale de la composition, et ledit ester d'acide gras et de saccharose est présent en une quantité de 0,1 à 50 % en masse sur la base de la quantité totale de la composition quand la composition est sous la forme d'administration orale, ou ledit acide organique est présent en une quantité de 0,1 à 30 % en masse sur la base de la quantité totale de la composition, et ledit ester d'acide gras et de saccharose est présent en une quantité de 0,1 à 20 % en masse sur la base de la quantité totale de la composition quand la composition est sous la forme d'une composition pour l'administration à la cavité orale ou
ledit acide organique est présent en une quantité de 30 à 90 % en masse sur la base de la quantité totale de la composition, et ledit ester d'acide gras et de saccharose est présent en une quantité de 5 à 50 % en masse sur la base de la quantité totale de la composition quand la composition est sous la forme d'une composition rapidement soluble pour l'administration à la cavité orale.

5. Utilisation selon la revendication 4 où la calcitonine est la calcitonine d'anguille [ASU^{1,7}].

6. Utilisation selon la revendication 4 où la composition est une composition pour l'administration orale.

7. Utilisation selon la revendication 4 où la composition est une composition pour l'administration sublinguale.

8. Utilisation selon la revendication 7 où la composition est une composition rapidement soluble.

Fig. 1

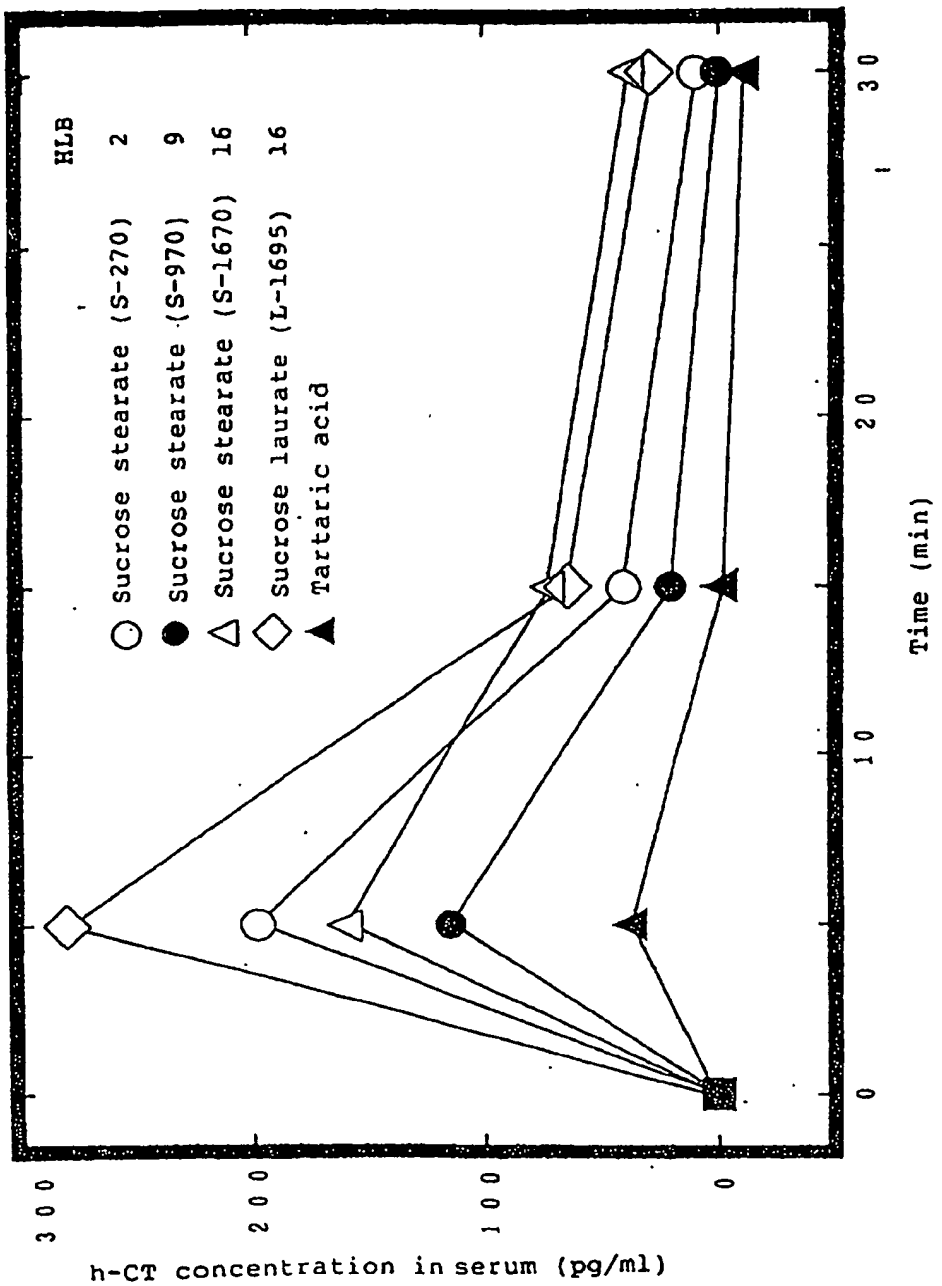

HLB
Sucrose stearate (S-270) 2
Sucrose stearate (S-970) 9
Sucrose stearate (S-1670) 16
Sucrose laurate (L-1695) 16
Tartaric acid
300
200
100
0
0
10
20
30
Time (min)
h-CT concentration in serum (pg/ml)

Fig. 2

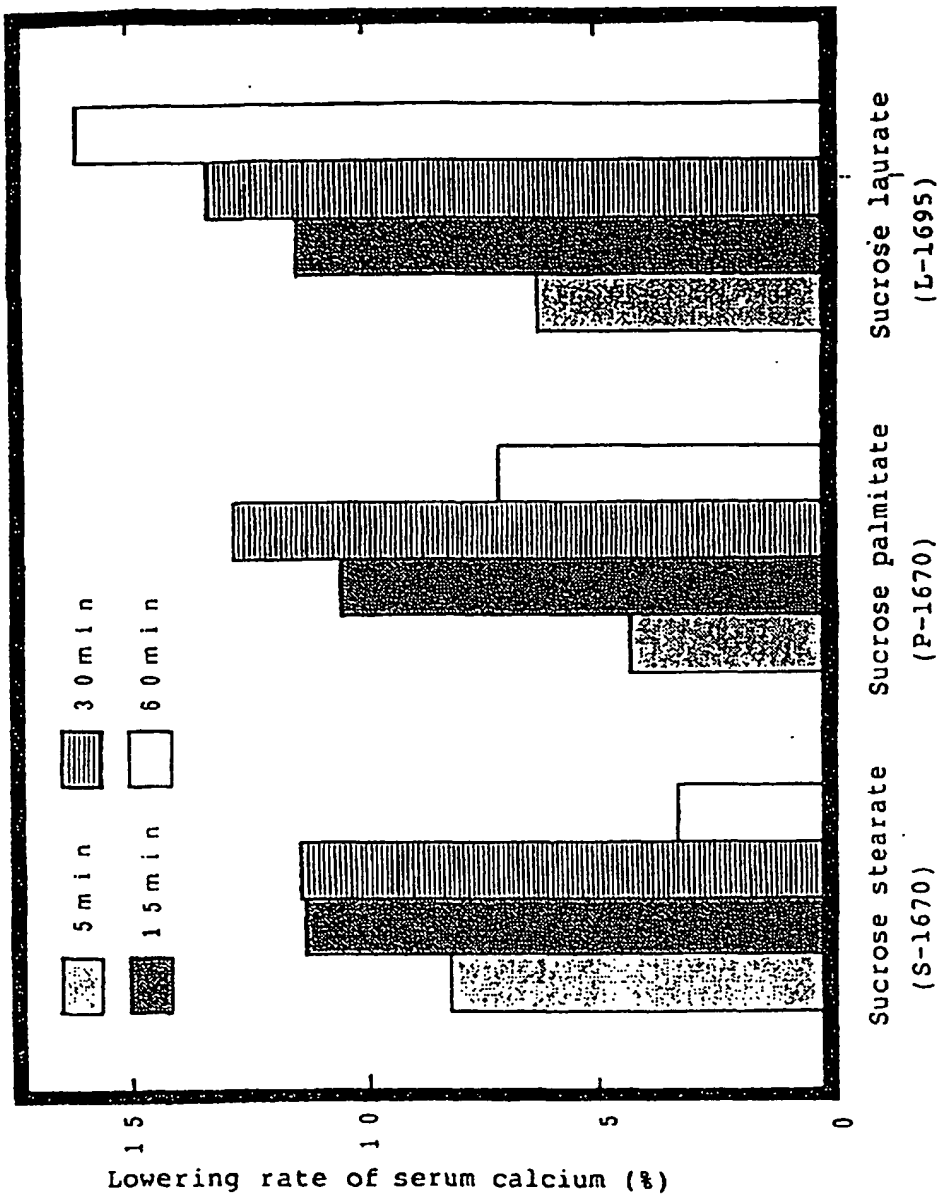

5 min
15 min
30 min
60 min
Sucrose stearate (S-1670)
Sucrose palmitate (P-1670)
Sucrose laurate (L-1695)
15
10
5
0
Lowering rate of serum calcium (%)

Fig. 3

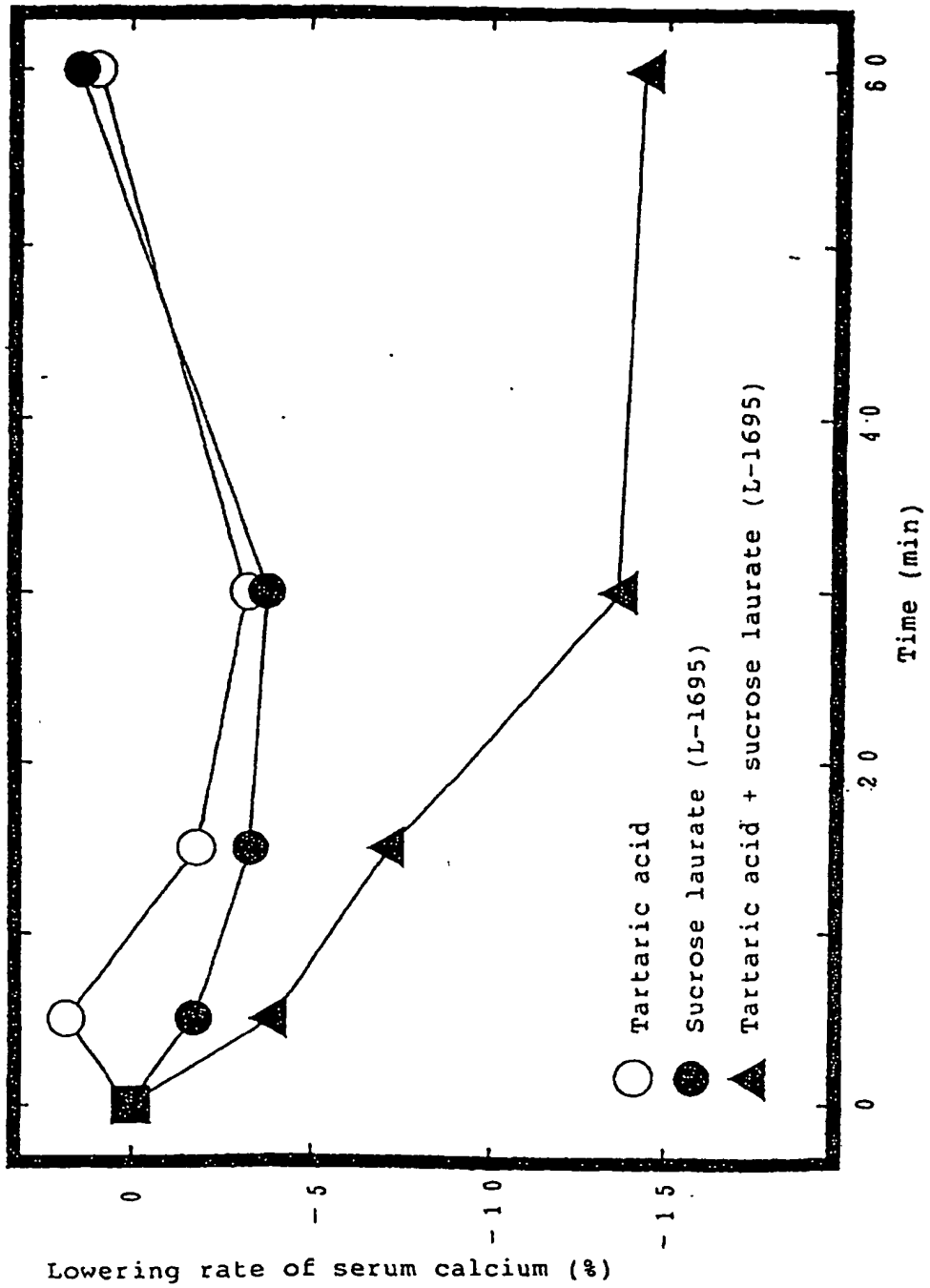

Lowering rate of serum calcium (%)
0
- 5
- 10
- 15
0
20
40
60
Time (min)
Tartaric acid
Sucrose laurate (L-1695)
Tartaric acid + sucrose laurate (L-1695)

Fig. 4

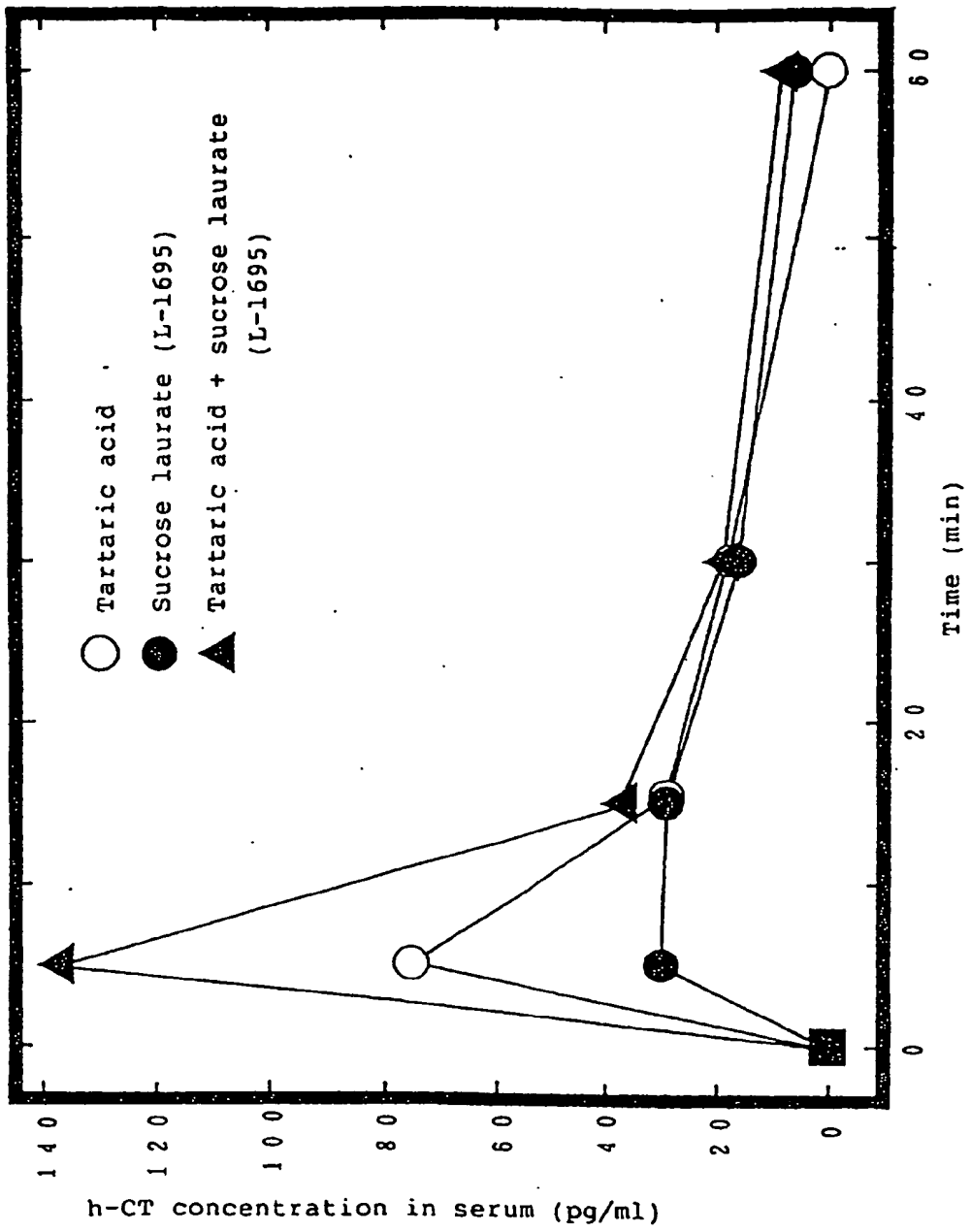

Tartaric acid
Sucrose laurate (L-1695)
Tartaric acid + sucrose laurate (L-1695)
h-CT concentration in serum (pg/ml)
0
20
40
60
80
100
120
140
0
20
40
60
Time (min)

Fig. 5

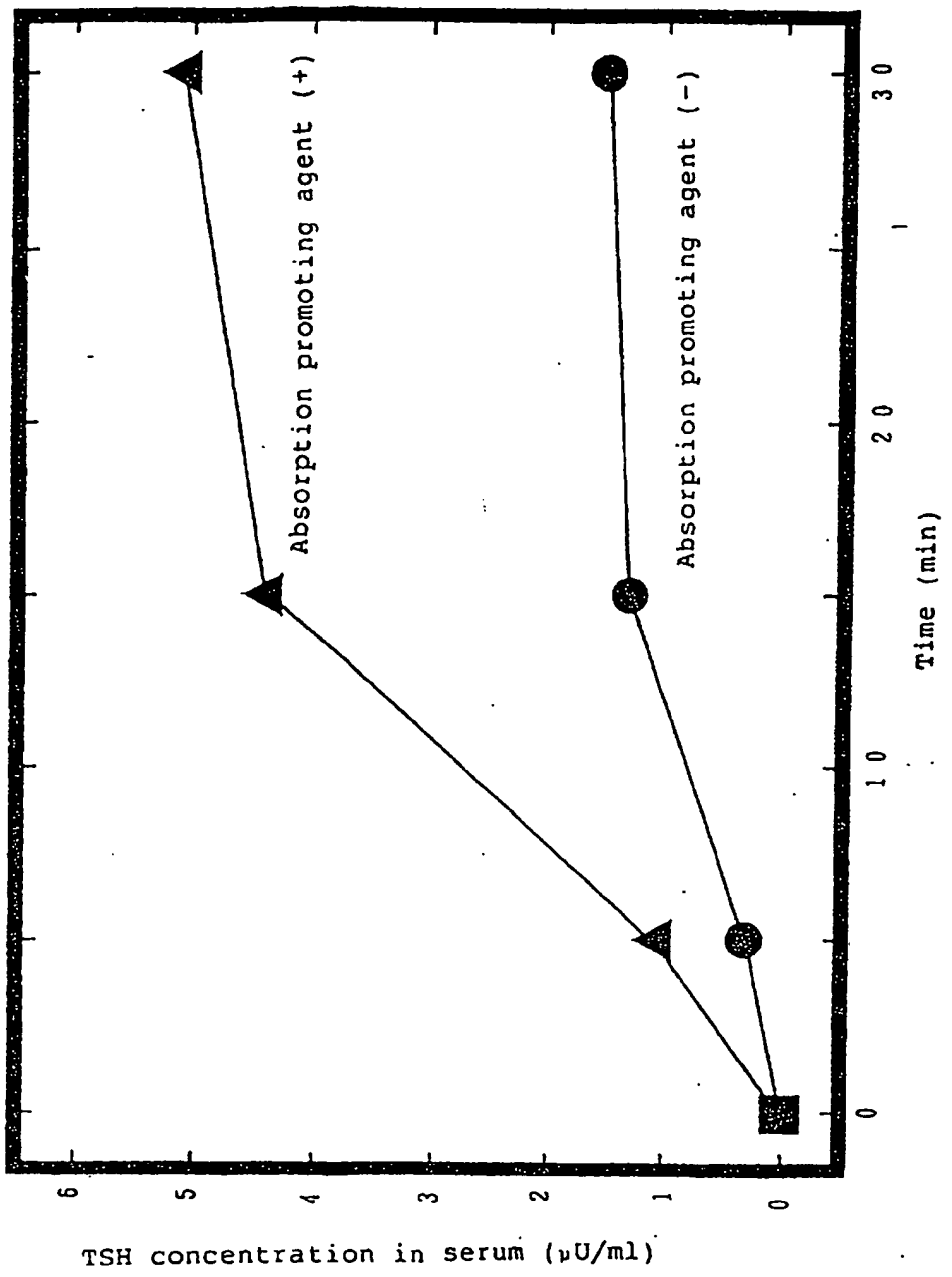
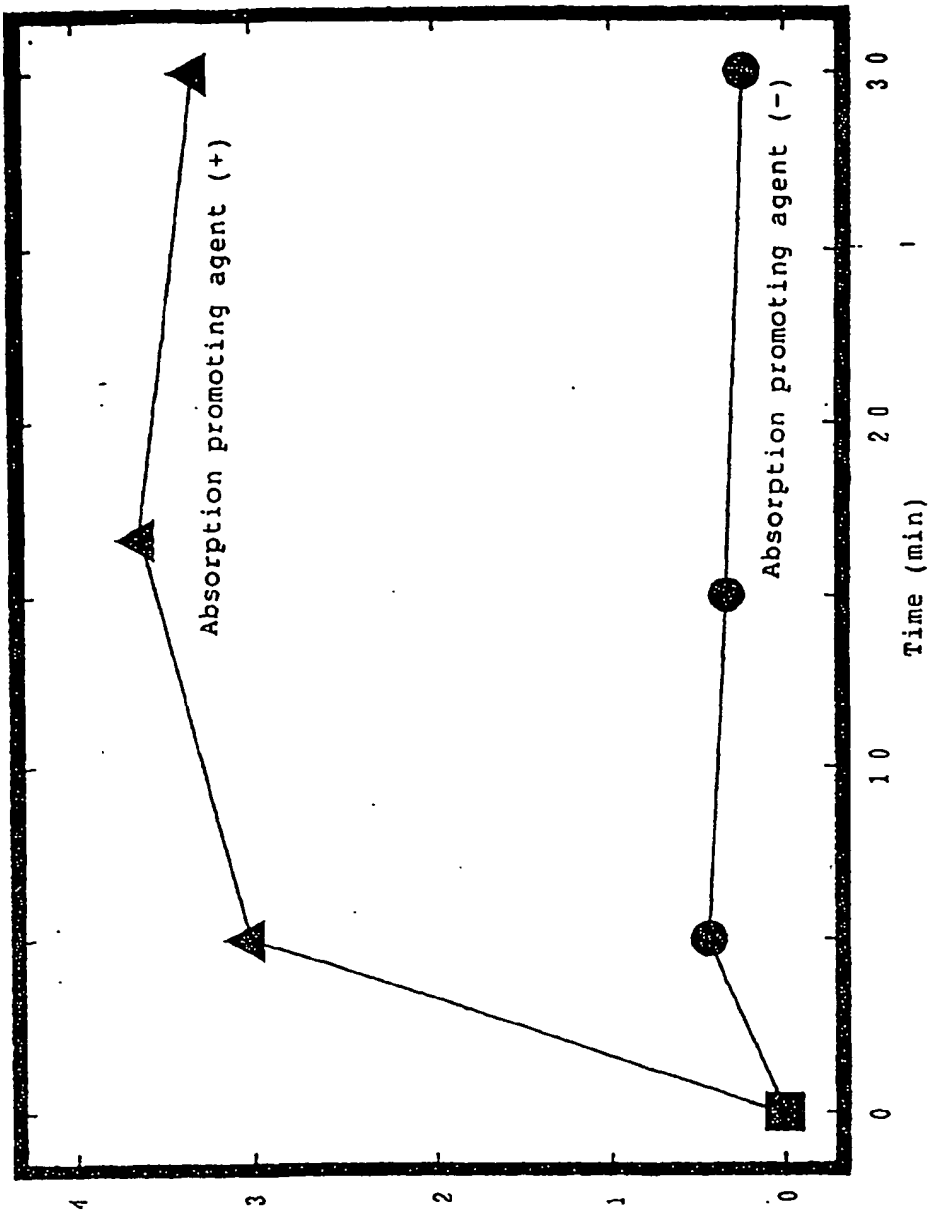

Absorption promoting agent (+)
Absorption promoting agent (-)
TSH concentration in serum (μU/ml)
Time (min)
0
1
2
3
4
5
6
10
20
30

Fig. 6


Absorption promoting agent (+)
Absorption promoting agent (-)
0
1
2
3
4
0
10
20
30
Time (min)
ACTH concentration in serum (ng/ml)

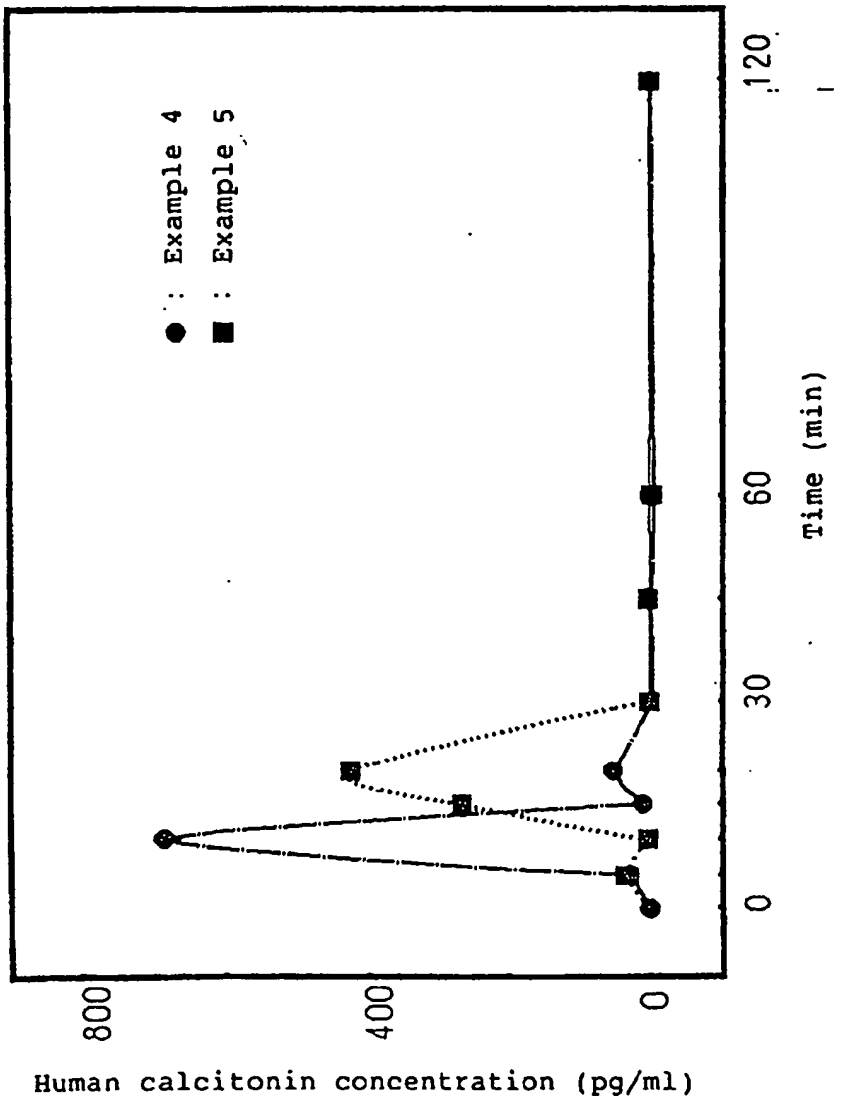

●: Example 4
■: Example 5
800
400
0
0
30
60
120
Time (min)
Human calcitonin concentration (pg/ml)

Fig. 7

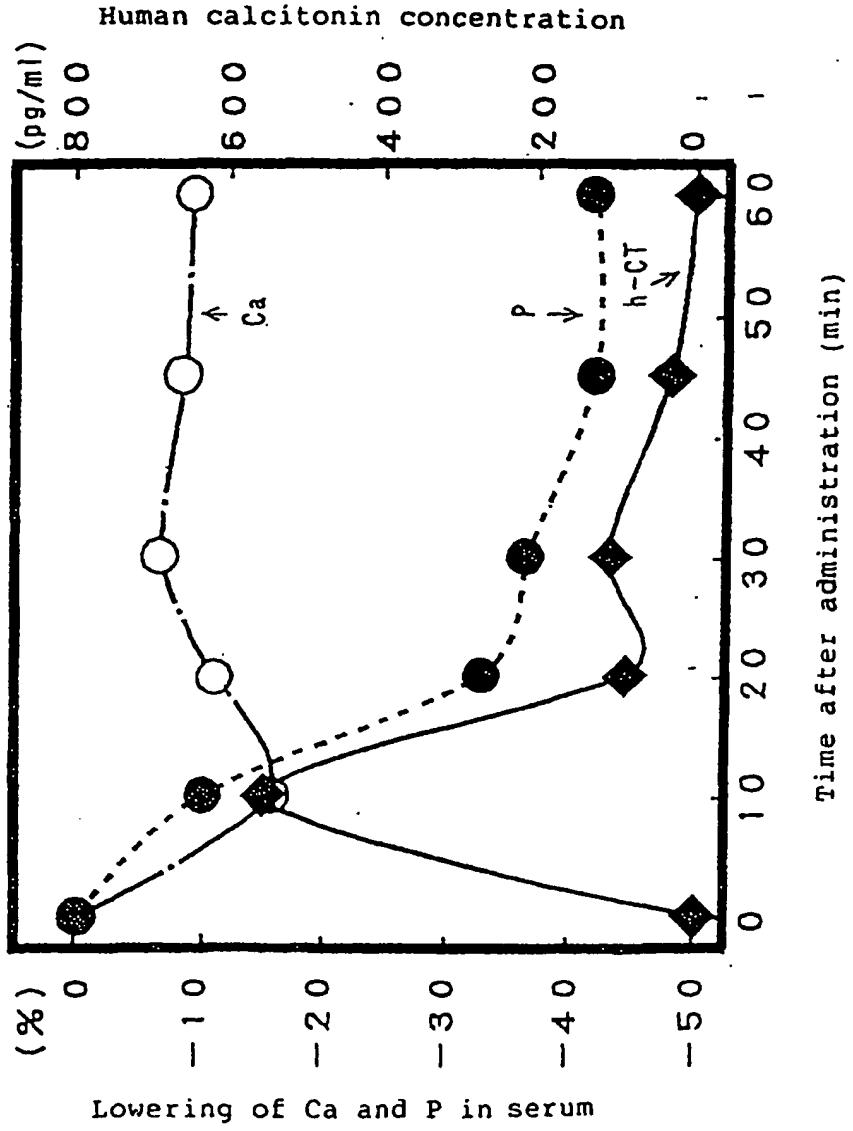

Human calcitonin concentration
(pg/ml)
800
600
400
200
0
Ca
P
h-CT
0
10
20
30
40
50
60
Time after administration (min)
(%)
0
-10
-20
-30
-40
-50
Lowering of Ca and P in serum

Fig. 8